CLAIMS

What Is Claimed Is:

1. A method of reducing toxicity of an orally administered therapeutic fused GABA analog, comprising:

making a fused GABA analog prodrug having a cleavable promoiety covalently bound to the therapeutic fused GABA analog;

placing the prodrug in a sustained release oral dosage form;

introducing the dosage form into the intestinal lumen of a patient by having the patient swallow the dosage form;

releasing the prodrug gradually into the intestinal lumen of the patient over a period of hours; and

cleaving the promoiety from the prodrug to provide a therapeutic concentration of the fused GABA analog in the plasma of the patient.

2. The method of Claim 1, wherein the toxicity of the fused GABA analog administered from said sustained release oral dosage form is less than the toxicity of an equivalent dose of the fused GABA analog administered from an immediate release oral dosage form.

3. The method of Claim 1, wherein the toxicity of the promoiety administered from said sustained oral release dosage form, and any metabolites thereof, is less than the toxicity of the promoiety, and any metabolites thereof, administered at an equivalent dose from an immediate release oral dosage form.

4. The method of any of Claims 1 to 3, wherein the promoiety metabolizes to form an aldehyde.

5. The method of Claim 4, wherein the aldehyde comprises formaldehyde.

6. The method of any one of Claims 1 to 3, wherein the promoiety metabolizes to form an acid that depletes carnitine in said patient.

7. The method of claim 6, wherein the acid comprises pivalic acid.

8. The method of Claim 1, wherein the period of hours comprises at least about 6 hours.

9. The method of Claim 1, wherein the period of hours comprises at least about 8 hours.

10. The method of Claim 1, wherein the period of hours comprises at least about 12 hours.

11. The method of Claim 1, wherein the dosage form releases from 0 to 20% of the prodrug in 0 to 2 hours, from 20 to 50% of the prodrug in 2 to 12 hours, from 50 to 85% of the prodrug in 3 to 20 hours and greater than 75% of the prodrug in 5 to 18 hours.

12. The method of Claim 1, wherein the concentration of the fused GABA analog in plasma of the patient over time provides a curve of concentration of the fused GABA analog in the plasma over time, the curve having an area under the curve (AUC) which is proportional to the dose of fused GABA analog administered.

13. The method of Claim 12, wherein the curve has a maximum plasma concentration (C_{max}) which is proportional to the dose of fused GABA analog administered.

14. The method of Claim 13, wherein the C_{max} is less than 75% of a C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form, and the AUC is at least 50% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

15. The method of Claim 13, wherein the C_{max} is less than 60% of a C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form, and the AUC is at least 75% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

16. The method of Claim 14, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

17. The method of Claim 15, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

18. An oral dosage form of a fused GABA analog prodrug, comprising:

a sustained release oral dosage form containing a fused GABA analog prodrug comprised of a therapeutic fused GABA analog covalently bound to a cleavable promoiety, the dosage form being adapted to be swallowed by a patient in order to introduce the dosage form into an intestinal lumen of the patient;

the dosage form further being adapted to release the prodrug gradually into the intestinal lumen of the patient over a period of hours after said swallowing, said gradual release causing the fused GABA analog to be cleaved from the promoiety after said swallowing and providing a therapeutic concentration of the fused GABA analog in the plasma of the patient.

19. The dosage form of Claim 18, wherein the promoiety metabolizes to form an aldehyde.

20. The dosage form of Claim 19, wherein the aldehyde comprises formaldehyde.

21. The dosage form of Claim 18, wherein the promoiety metabolizes to form an acid that depletes carnitine in said patient.

22. The dosage form of Claim 21, wherein the acid comprises pivalic acid.

23. The dosage form of Claim 18, wherein the period of hours comprises at least about 6 hours.

24. The dosage form of Claim 18, wherein the period of hours comprises at least about 8 hours.

25. The dosage form of Claim 18, wherein the period of hours comprises at least about 12 hours.

26. The dosage form of Claim 18, wherein the dosage form releases from 0 to 20% of the prodrug in 0 to 2 hours, from 20 to 50% of the prodrug in 2 to 12 hours, from 50 to 85% of the prodrug in 3 to 20 hours and greater than 75% of the prodrug in 5 to 18 hours.

27. The dosage form of Claim 18, wherein the dosage form, upon swallowing, provides a curve of concentration of the fused GABA analog in the plasma over time, the curve having an area under the curve (AUC) which is proportional to the dose of fused GABA analog administered.

28. The dosage form of Claim 27, wherein the curve has a maximum plasma concentration (C_{max}) which is proportional to the dose of fused GABA analog administered.

29. The dosage form of Claim 28, wherein the C_{max} is less than 75% of a C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form and the AUC is at least 50% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

30. The dosage form of Claim 28, wherein the C_{max} is less than 60% of a C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form, and the AUC is at least 75% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

31. The dosage form of Claim 29, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

32. The dosage form of Claim 30, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

33. The dosage form of Claim 18, wherein the dosage form comprises an osmotic dosage form.

34. The dosage form of Claim 18, wherein the dosage form comprises a prodrug-releasing polymer.

35. The dosage form of Claim 18, wherein the dosage form comprises a prodrug-releasing lipid.

36. The dosage form of Claim 18, wherein the dosage form comprises a prodrug-releasing wax.

37. The dosage form of Claim 18, wherein the dosage form comprises tiny timed-release pills.

38. The dosage form of Claim 18, wherein the dosage form comprises prodrug releasing beads.

39. A method of orally administering a fused GABA analog prodrug, comprising:

making a fused GABA analog prodrug having a cleavable promoiety covalently bound to the therapeutic fused GABA analog;

placing the prodrug in a sustained release oral dosage form;

introducing the dosage form into the intestinal lumen of a patient by having the patient swallow the dosage form;

releasing the prodrug gradually from the swallowed dosage form into the intestinal lumen of the patient over a period of hours; and

allowing the fused GABA analog to be cleaved from the promoiety after said swallowing to provide a therapeutic concentration of the fused GABA analog in the plasma of the patient.

40. The method of Claim 39, wherein the promoiety metabolizes to form an aldehyde.

41. The method of Claim 40, wherein the aldehyde comprises formaldehyde.

42. The method of Claim 39, wherein the promoiety metabolizes to form an acid that depletes carnitine in said patient.

43. The method of claim 42, wherein the acid comprises pivalic acid.

44. The method of Claim 39, wherein the period of hours comprises at least about 6 hours.

45. The method of Claim 39, wherein the period of hours comprises at least about 8 hours.

46. The method of Claim 39, wherein the period of hours comprises at least about 12 hours.

47. The method of Claim 39, wherein the dosage form releases from 0 to 20% of the prodrug in 0 to 2 hours, from 20 to 50% of the prodrug in 2 to 12 hours, from 50 to 85% of the prodrug in 3 to 20 hours and greater than 75% of the prodrug in 5 to 18 hours.

48. The method of Claim 39, wherein the concentration of the fused GABA analog in plasma of the patient over time provides a curve of concentration of the fused GABA analog in the plasma over time, the curve having an area under the curve (AUC) which is proportional to the dose of fused GABA analog administered.

49. The method of Claim 39, wherein the curve has a maximum plasma concentration (C_{max}) which is proportional to the dose of GABA analog administered

50. The method of Claim 48 or 49, wherein the C_{max} is less than 75% of the C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form and the AUC is at least 50% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

51. The method of Claim 48 or 49, wherein the C_{max} is less than 60% of the C_{max} obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form and the AUC is at least 75% of an AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

52. The method of Claim 50, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

53. The method of Claim 51, wherein the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.